REMARKS/ARGUMENTS

Claims 1-7 are pending in the instant application. Claims 1, 2, 4 and 7 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to point out and claim the subject matter. Claims 1, 2, 4, and 7 stand rejected under 35 U.S.C. 102 (b) as being anticipated by Mattrey (WO00/45855). Further, claims 1-7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mattrey (WO00/45855) in view of Dugstad et al (US 6,221,337).

Claim 1 has been amended to more specifically claim what the Applicant regards as the invention, by specifying that the shell comprises negatively charge phospholipids in an amount of from 50-100%. Basis is found in cancelled claim 5. Claims 3 and 4 have also been cancelled. Reconsideration is respectfully requested.

Claim rejections – 35 USC §112

The method to determine the stability is described on pages 7 and 8 of the current application description. The term "pressure stability of at least 50%" means that the acoustic attenuation efficacy of the microbubbles after being exposed to a pressure of 120 mm Hg is at least 50% of the acoustic attenuation efficacy of said microbubbles before being exposed to said pressure. The Applicant also submits that claim 1 has been amended to more specifically claim the invention. Applicants therefore respectfully request that the rejection of claims 1-7 under 35 USC 112 be removed.

Claim rejections 35 USC § 102 and 103

Claims 1, 2, 4, and 7 stand rejected under 35 U.S.C. 102 (b) as being anticipated by Mattrey (WO00/45855). Further, claims 1-7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Mattrey (WO00/45855) in view of Dugstad et al (US 6,221,337).

The Examiner states that Mattrey discloses use of an ultrasound agent which has a mean particle size of about 0.25-15 μm in diameter and a pressure stability of at least 50 % at a pressure of 120 mmHg. The Applicant respectfully disagrees. When claim 1 of the present application states that the contrast agent has a pressure stability of 50 % at 120 mmHg, this means that at least 50 % of the microbubbles would survive, i.e. not collapse, and maintain their acoustic attenuation efficacy at an overpressure of 120 mmHg. Several factors are decisive for the stability of the microbubbles, including both the gas and the shell material of the microbubble. Mattrey does suggest various ultrasound contrast agents, but the Applicant fails to see that Mattrey is describing what the stability level of preferred such contrast agents should be. Mattrey does not suggest what the stability of microbubbles should be which are appropriate for use in lymph node imaging. Further, Mattrey does not disclose microbubbles wherein the shell comprises negatively charge phospholipids in an amount of from 50-100%. Hence, Mattrey fails to disclose each and every essential feature of claim 1, and cannot be used as a 35 USC 102(b) rejection for claims 1, 2, and 7 (claim 4 has been cancelled).

On page 16 Mattrey lists a long range of contrast agents claimed to be suitable for use in methods for identifying the sentinel lymph node. This list includes Albunex®, which was shown by Applicants Example 1 of the instant application not to fall within the required high

stability of the microbubbles of the present Claim 1. Example 3 of Applicants description illustrates that Albunex is not suitable for use in a method for identification of a sentinel lymph node. Applicants find that the present invention is a selection under Mattrey. The invention, with amended claim 1, has been restricted to a method using microbubbles having a shell which comprises of 50 to 100 % negatively charged phospholipids. Mattrey does not mention a restriction to such microbubbles. The contrast agents mentioned by Mattrey, page 16, comprise mainly of microbubbles of proteins (Albunex®, Optison®, Quantison®), cyanoacrylate (Sonovist®), palmitic acid (Levovist®) or a surfactant (Echogen®), in addition to at least a gas. Of the microbubbles comprising phospholipids a majority of these comprise at least 50 % neutral phospholipids, for example lecitins such as phosphatidylcholines (Aerosomes, MRX115 (Definity®)). The example presented in Mattrey uses Imagent® (AF0150) comprising dimyristoylphosphatidylcholine, which is a neutral phospholid, and starch, and fall outside the scope of the instant claims. Applicants find that a method for identification of a sentinel lymph node in a subject comprising administering microbubbles with the combination of a stability of at least 50 % at a pressure of 120 mm Hg and a specified composition of at least 50 % negatively charged phospholipids is a novel selection invention over Mattrey. Hence, Applicants disagree that Mattrey discloses that the pressure stability of the microbubbles should be at least 50 % at 120 mmHg, and there is no guidance from Mattrey for the use of a certain type of microbubbles with such high stability.

. It is well settled in case law that prior patents are references only for what they clearly disclose or suggest. Additionally, it is not proper use of a patent as a reference to

modify its structure to one which prior art references do not suggest. *In re Randol and Redford*, 425 F.2d 1268, 165 U.S.P.Q. 586, 588 (C.C.P.A. 1970). A reference must be considered not just for what it expressly teaches, but also for what it fairly suggests to one who is unaware of the claimed invention. *In re Baird*, 16 F.3d 380, (Fed. Cir. 1994).

Dugstad et al discloses ultrasound contrast agents comprising microbubbles wherein predominantly charged phospholipids is essentially the sole amphiphilic component, and suggest that such may convey valuable benefits in terms of stability and acoustic properties. The Dugstad et al patent covers the contrast media Sonazoid™ of the Applicant. There is no suggestion by Dugstad to use such microbubbles in the imaging of lymph nodes, or for the discrimination between benign and malignant such. Hence, Applicant believes it would not be obvious for the ordinary skilled in the art to combine the methods of Mattrey with the teaching related to the composition of the stabile microbubbles of Dugstad, as Mattrey does not point in the direction of particularly stable microbubbles. There is simply no reason provided by Mattrey for the skilled person to select the specific group of contrast agents as claimed. Further, numerous types of contrast agents for ultrasound imaging are disclosed in the state of art of various sizes, different stability properties and of many different types of materials. Dugstad discloses microbubbles stabilised by phospholipids. The Applicant respectfully submits that the combination of the microbubbles disclosed by Dugstad with the method disclosed by Mattrey, properly addressing all limitations of the instant claims, can only be made with the benefit of hindsight. Applicants respectfully again submit that it is not proper use of a patent as a reference to modify its structure to one which prior art references do not suggest. *In re Randol and Redford*, 425 F.2d 1268, 165 U.S.P.Q.

586, 588 (C.C.P.A. 1970). A reference must be considered not just for what it expressly teaches, but also for what it fairly suggests to one who is unaware of the claimed invention. *In re Baird*, 16 F.3d 380, (Fed. Cir. 1994).

Hence, the Applicant believes claims 1-7 are not obvious in relation to the prior art, viewed alone or in combination.

In view of the remarks hereinabove, Applicants submit that the instant application, including claims 1, 2, 6 and 7 is in condition for allowance. Favorable reconsideration is respectfully requested.

Respectfully submitted,

/Craig Bohlken/
Craig Bohlken
Reg. No. 52,628

GE Healthcare, Inc.
101 Carnegie Center
Princeton, NJ 08540
Phone (609) 514-6530